REMARKS

Introductory Comments

Applicant notes with appreciation the withdrawal of the finality of the previous Office Action. The present Office Action replaces the Action mailed June 17, 2008. Applicant notes the Office Action Summary of the present Office Action indicates the Action is both final and non-final (see boxes 2a and 2b of the Office Action Summary). However, the Examiner told applicant's representative that the reissued Office Action would be non-final and the reissued Action indicates at pages 2 and 8 that it is non-final. Moreover, PAIR describes the Action as non-final. Accordingly, applicant assumes the Action is indeed non-final.

The amendments and remarks submitted herewith are the same as those filed September 17, 2008. Additionally, applicant is resubmitting the Information Disclosure Statement that accompanied the response filed September 17, 2008.

Claims 1-3, 6, 7, 10-12, 15-21, 41 and 43-45 were examined in the Office Action. Claims 1-3, 6, 7, 10-12, 15-21 and 41 stand rejected under 35 U.S.C. §103(a). Applicant notes with appreciation the withdrawal of the previous rejections of record.

Overview of the Above Amendments

Claims 10, 11, 20 and 21 have been canceled and claims 1, 3 and 41 have been amended to recite that the HCV immunogen is peptide p214K9. Support for this amendment can be found at page 13, lines 6-8. As explained in the specification, this peptide is an immunodominant, H-2^K-restricted, HCV-1a-NS5a-specific CTL epitope which contains a nine amino acid stretch of the NS5a protein (residues 2152-2160). Lee et al., *Vaccine* (2000) 18:1962-1968, referenced in the present application at page 13, line 9, explains that this epitope has the sequence HEYPVGSQL. See, page 1964, column 2, last two sentences of Lee which accompanies the Information Disclosure Statement submitted herewith.

Amendment and cancellation of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing the canceled or unamended claims.

35 U.S.C. § 103

Claims 1-3, 6, 7, 10-12, 15-19, and 41[1] were rejected under 35 U.S.C. §103(a) as being unpatentable over Gorczynski et al., *Cellular Immunol.* (1995) 160:224-231 ("Gorczynski"), in view of U.S. Patent No. 6,582,692 to Podsakoff et al., ("Podsakoff") and further in view of Wakita et al., *J. Biol. Chem.* (1998) 273:9001-9006 ("Wakita"). Gorczynski is cited for teaching a method of making a mouse that is tolerant to skin allografts by injecting cells into the portal vein of the mouse. The Office correctly notes Gorczynski does not teach the delivery of a nucleic acid encoding a protein. Podsakoff allegedly teaches sustained expression of a gene of interest in the liver of an animal following portal vein administration by AAV-mediated gene delivery using a liver specific promoter and enhancer. Wakita is cited for teaching that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a trangenic mouse results in an animal that can be used as a tool to investigate the immune responses and pathogenesis of HCV infection. The Office argues:

> [I]t would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

Office Action, page 4. However, applicant respectfully submits the Office has failed to provide a *prima facie* case of obviousness.

Initially, applicant notes claims 20 and 21 were not subject to this rejection. These claims recite that the immunogen is the NS5a protein of HCV and depend from rejected claims 16 and 17, respectively which in turn depend from claims 1 and 3, respectively. Claims 1 and 3 have been amended to incorporate the recitation that the immunogen is peptide p214K9. As explained above, this immunogen is an NS5a epitope. Thus, at least claims 16 and 17, and claims 18 and 19 which depend therefrom, should no longer be subject to this rejection and withdrawal of the rejection with respect to claims 16-19 is respectfully requested.

Regarding the remaining claims, applicant respectfully traverses the rejection as follows. The Examiner has stated the Declaration of Michael Houghton Ph.D., submitted with the

response dated October 30, 2007, is not applicable to the new rejections. However, applicant disagrees. In fact, Dr. Houghton's Declaration is highly relevant and should be considered *vis-a-vis* the newly stated art combinations. As explained in paragraph 7 of Dr. Houghton's Declaration, there remains a need in the art for suitable animal models to screen for agents capable of modulating or reversing immunological tolerance to HCV antigens. Such a long-felt need is a secondary consideration that is in fact an *indicia* of nonobviousness sanctioned by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (US 2007) and *Graham v. John Deere Co.*, 148 USPQ 459 (US 1966). See, also, *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, 86 USPQ2d 1196, 1202 (Fed. Cir. 2008). Despite the failure of others, applicant has discovered a successful method for preparing a non-human animal for screening for agents that modulate tolerance to an HCV immunogen by exogenously delivering a nucleic acid directing liver-specific expression of an HCV immunogen to the liver of the animal by portal vein injection. For this reason alone, the rejection of the claims over the stated combination should be withdrawn.

Moreover, Dr. Houghton explains in paragraph 7 of the Declaration that HCV replication occurs almost exclusively in the liver where tolerance to the virus develops due to the specialized liver environment, which limits T cell activation and function. It is Dr. Houghton's opinion that both Gorczynski and Wakita fail to describe such a system.

In particular, Gorczynski fails to describe HCV, let alone the p214K9 peptide now claimed. As explained in paragraph 6 of Dr. Houghton's Declaration, Gorczynski describes the injection of lymphoid or spleen cells into the portal veins of mice a few days prior to skin graft transplants in order to delay rejection and fails to describe anything pertaining to HCV. Moreover, the cellular antigens are not restricted to the liver and can migrate elsewhere. Accordingly, Gorczynski's animal model exposes antigens to the host's immune system outside of the tolerogenic environment of the liver, unlike the present invention where expression of HCV antigens is restricted to the liver and thus better mimics the natural biology of the HCV virus and the evolution of tolerance. See, paragraph 9 of Dr. Houghton's Declaration.

[1] Applicant notes claims 43-45 were not subject to any rejections. However, the Office Action Summary indicates that these claims are also rejected. Clarification is therefore requested.

Wakita's transgenic mice, although expressing HCV cDNA are also deficient. As with Gorczynski, there is no discussion whatsoever regarding HCV NS5a, let alone the p214K9 epitope. Additionally, as explained in paragraph 8 of Dr. Houghton's Declaration, unlike the animal model of the instant invention, expression of HCV antigens in the transgenic animal model described by Wakita is not liver-specific. Genes encoding HCV antigens are present in every tissue of the transgenic mice and are expressed using a promoter that is not liver-specific. Furthermore, the adenovirus vector encoding the Cre trans gene, which is used to turn on expression of genes encoding HCV antigens is not restricted to the liver. Rather, expression of HCV antigens is detected in a variety of tissues outside of the liver in Wakita's transgenic mice, including in the lung, spleen, thymus, kidney, stomach, intestines, and muscles (see page 9004, col. 1). Moreover, in the CN2-29 transgenic mice described by Wakita, the expression of the HCV core antigen is at about the same level in the spleen (5.5 ng/mg) as in the liver (6.6 ng/mg) and only about 2-fold less in the lung (2.9 ng/mg). Thus, the transgenic mice of Wakita express HCV antigens in multiple tissues where immunoreactivity is not dampened in the same way as the liver.

Dr. Houghton in paragraph 10 also explains that a transgenic mouse, such as described by Wakita, makes a less desirable animal model of immunological tolerance due to the presence of antigens at birth. In particular, the immune system views antigens present at birth as "self" antigens and produces long term immunological tolerance to self-antigens by thymic deletion of T cells specifically immunoreactive with those antigens. In contrast, the later development of tolerance to non-self antigens by exposure of antigens in the liver has a different underlying mechanism. Therefore, animal models in which antigens are expressed at birth do not provide a good model of tolerance to non-self antigens as develops from exposure of antigens in the liver later in life.

Moreover, as explained above and also detailed in paragraph 11 of Dr. Houghton's Declaration, even though Wakita uses a Cre/loxP system to control expression of HCV antigens, genes encoding the HCV antigens are present in every tissue of the animal and expressed at some level in a variety of tissues outside of the liver. Thus, in these transgenic animals, the immune system may be exposed to HCV antigens due to leaky expression of viral genes, albeit at a low level, from birth. In contrast, the instant application provides a non-germline animal model of

tolerance that more accurately mimics the natural development of tolerance during chronic HCV infection.

In addition, as explained in paragraph 12 of Dr. Houghton's Declaration, it is much more expensive and time consuming to produce numerous transgenic animals, as described by Wakita, for screening for agents that modulate immunological tolerance. The use of portal vein injection of nucleic acids encoding HCV immunogens, as described in the present application, greatly facilitates screening. Various immunodominant HCV epitopes can be rapidly screened by this method for the development of immunological tolerance and agents that relieve tolerance. Thus, this method greatly increases the ease and flexibility of screening. In contrast, producing a dozen or more transgenic animals, as described by Wakita, to test the same epitopes would entail a great deal more effort, expense, and time.

In sum, the animal model of the instant invention presents numerous advantages over those described by Gorczynski and Wakita for screening for agents that modulate tolerance to HCV immunogens.

Podsakoff does not cure the deficiencies of Gorczynski and Wakita. In this regard, Podsakoff pertains to gene therapy, not immunological tolerance. In particular, Podsakoff relates to the delivery of genes coding for lysosomal storage enzymes missing or defective in a patient and does not describe immunological tolerance or methods of preparing an animal model for screening for agents that modulate tolerance to an HCV immunogen. Lysosomal storage enzymes are not immunogens, but rather, endogenous proteins which are synthesized in the spleen and liver. Thus, these enzymes would not be expected to produce an immune response and cannot be used to produce an animal model of immunological tolerance. Additionally, there would be a presumption of success in expressing lysosomal enzymes in the liver that cannot be extrapolated to other genes not normally expressed there. Podsakoff fails to teach or suggest any method for inducing tolerance to antigens in an animal model, as claimed. Finally, as with the other cited references, Podsakoff does not describe the use of proteins from the NS5a region of the HCV genome, and certainly does not teach or suggest the peptide p214K9.

Based on the foregoing, applicant respectfully submits the claims are in fact patentable over the cited combination and withdrawal of the rejection over Gorczynski, in view of Podsakoff and Wakita is respectfully requested.

Claims 1-3, 6, 7, 10-12, 15-21, and 41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gorczynski in view of Podsakoff, further in view of Wakita, and further in view of PCT Publication No. WO 97/47358 to Donnelly et al. ("Donnelly"). Gorczynski, Podsakoff and Wakita are applied as above. Donnelly is cited for allegedly teaching that a nucleic acid encoding HCV NS5a could be used to raise an immunological response to HCV in an animal. However, applicant submits the cited combination fails to render the present claims obvious.

The combination of Gorczynski, Podsakoff and Wakita is discussed above. In particular, neither Gorczynski nor Podsakoff describe HCV NS5a proteins, let alone the p214K9 peptide which is recited in all of applicant's claims. Moreover, neither Gorczynski nor Podsakoff have anything to do with methods of preparing an animal model for screening for agents that modulate tolerance to an HCV immunogen. On the contrary, Gorczynski pertains to methods of delaying transplant rejection of skin allografts by injection of lymphoid or spleen cells into the portal vein of an animal. Podsakoff relates to gene therapy and is also not relevant to the presently claimed invention. Podsakoff has nothing to do with immunological tolerance or methods of preparing an animal model for screening for agents that modulate tolerance to an HCV immunogen. As with Gorczynski and Podsakoff, Wakita fails to teach or suggest the NS5a p214K9 epitope. Additionally, Wakita's transgenic mice, although expressing HCV cDNA, are deficient. Even though Wakita uses a Cre/loxP system to control expression of HCV antigens, genes encoding the HCV antigens are present in every tissue of the animal and expressed at some level in a variety of tissues outside of the liver. In contrast, the instant application provides a non-germline animal model of tolerance that more accurately mimics the natural development of tolerance during chronic HCV infection.

Donnelly does not cure the defects of Gorczynski, Podsakoff and Wakita. Donnelly has nothing to do with immunological tolerance to HCV. To the contrary, the focus of Donnelly is on therapeutic and prophylactic vaccines capable of eliciting an immune response against HCV. Thus, Donnelly describes methods for inducing immunity against HCV, which is the opposite of immunological tolerance. Additionally, although Donnelly includes a sequence for HCV NS5a, Donnelly does not teach or suggest the NS5a p214K9 epitope that is present in all of the claims.

In this case, the combination of Gorczynski, Podsakoff, Wakita, and Donnelly fails to teach or suggest the method of the claimed invention, including in particular, the injection of a nucleic acid directing liver-specific expression of an HCV immunogen into the portal vein of an animal wherein the HCV immunogen is peptide p214K9. Thus, the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). Rather, as explained above, the evidence is to the contrary.

Applicant submits the Examiner has chosen bits and pieces of the cited references to arrive at the allegation that this combination of references suggests the claimed invention. This is improper. As stated in *KSR*, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, page 1396. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Thus, a rejection cannot be predicated on the mere identification of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner.

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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